REMARKS

I. Status of the Application and Claims

With entry of this Amendment, claims 13, 26, and 52-85 are pending in the application. Applicants have canceled, without prejudice or disclaimer, non-elected claims 3, 4, 6-12, 15-25, 29, 32-35, 38-41, and 43-51. They reserve the right to pursue the subject matter of those claims in one or more divisional applications.

Applicants have amended claim 26 solely to more clearly recite their invention. Support for the amendment is found in the specification at, for example, original claim 13 of PCT/US99/20011, and page 7. No new matter is entered by the amendment.

Applicants acknowledge that the Office has vacated the Notice of Non-Compliance mailed January 21, 2004. Office action, page 2.

Applicants acknowledge that the restriction requirements set forth in the Office actions mailed September 9, 2002, and April 22, 2003, have been made final. *Id.*, page 3. In due course, Applicants will file a petition with the Commissioner seeking review of the restriction requirement as set forth in the April 22, 2003, Office action.

The Office objects to the specification because the "Brief Description of the Drawings" refers to parts A and B of Figure 6, but Figure 6 is not so labeled. *Id.* Applicants are submitting with this Amendment one revised sheet of drawings wherein the panels of Figure 6 have been properly identified as "A" and "B." No new matter has been entered into the application by the amendment to the drawings. Hence, Applicants request withdrawal of the objection.

The Office objects to claims 26, 52, 70-80, 82, 83, and 85 for reciting or encompassing non-elected inventions. Office action, page 4. The Office also objects to

claims 70, 82, 83, and 85 because they depend from non-elected claims. *Id.* Applicants request the Office to hold those issues in abeyance pending decision by the Commissioner of Applicants' petition seeking review of the April 22, 2003, restriction requirement.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

A. The Specification Enables the Full Scope of the Claims

Claims 26, 52, 70-80, 82, 83, and 85 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while admittedly "enabling for a method of screening for ligands of GPRC's, using a host cell comprising the mutated G-proteins listed in the instant Specification (the 3-5 positive mutations in Table 1 and 2, or Table 3)," allegedly "does not enable [the] use of cells comprising mutations in unspecified cell proteins, or comprising *all* G-protein mutations, including those not yet tested." The Office also contends that "[t]he Specification is not enabling for use of those mutations that would be ineffective in the disclosed assays and those that would have the opposite effects than claimed." Office action, page 4. Based on this reasoning, the Office concludes that the scope of enablement is not commensurate with the scope of the claims. *Id.*, page 5. Applicants traverse the rejection.

In making the rejection, the Office raises several of the factors mentioned in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). For example, citing to a number of published articles, including two published after Applicants' filing date,[1] the Office

[1] "In general, the examiner should not use post-filing date references to demonstrate that the patent [*sic*, specification] is nonenabling." M.P.E.P. § 2164.05(a). An exception is where the reference provides evidence of what one skilled in the art would have

concludes that "[t]hese examples and others illustrate that it is not predictable as to which amino acid mutations or deletions are necessary to produce a G-protein subunit with the claimed characteristics." Office action, page 6. Thus, the Office concludes that "the predictability of the art is low with regards to the knowledge of what effects altering the sequence of a G-protein polypeptide would have on the usefulness of that polypeptide[] in the claimed methods." *Id.* Absolute predictability, however, is not the standard for enablement. If it were, then any experimentation needed to make and use an invention would render the claimed invention nonenabled. "The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." Because there is some element of unpredictability in any aspect of biology, some experimentation may be needed. Here, however, that experimentation is routine given the teaching of Applicants' specification.

The level of skill in the art, a factor that must be considered under *Wands*, is high. And even if the experimentation involved is complex, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. § 2164.01. The experimentation involved here is the introduction of mutations into a know nucleotide sequence encoding a GPCR and then screening the mutants for the desired activity. Applicants submit that routine screening, even if complex, does not constitute undue experimentation. Screening for a desired mutation is a natural consequence of biological unpredictability, and thus routine.

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known on or before the filing date. That exception does not apply to the cited post-filing date references.

Moreover, to the extent there is unpredictability pertaining to the usefulness in the claimed method of any given mutation in a GPCR, there is guidance in the specification that directs one to particular regions of the GPCR to mutate. For example, page 12, lines 8-17, and pages 13-15, identify a number of different regions in GPCRs that play a role in GPCR activation. One of skill in the art would expect mutations in those regions to be useful in the claimed invention. Thus, the Office's assertions that "there is no guidance or working examples . . . as to what amino acids in the G-protein subunit are necessary to cause an increase in cell responsiveness due to agonist" and "there is no guidance regarding which deletions in the G-protein subunit are tolerated while maintaining the claimed functional characteristics" are not supported by the disclosure in the specification.

As part of the evidence it relies on in concluding the specification does not enable the full scope of the claims, the Office mentions "the absence of working examples directed to all encompassed subunits." Office action, page 7. While the presence or absence of working examples is a *Wands* factor, there is no requirement that a specification include working examples to all embodiments within the scope of a claim to satisfy the enablement requirements.

The Office states that "[t]he specification is not enabling for use of those mutations that would be ineffective in the disclosed assays and those that would have opposite effects than claimed." Office action, page 4. Respectfully, any concerns over ineffective mutations or those having opposite effects than claimed are misplaced. A specification, coupled with the level of skill in the art, must enable the skilled artisan to

practice the claimed invention with undue experimentation. There is no requirement in the law to enable what is not being claimed.

In the Office's view, the scope of enablement is limited to the particular mutations introduced using SEQ ID NOs: 42-63 that produce a positive effect on cell growth when tested. *See* Office action, page 5. Applicants respectfully disagree. Given the skill in the art and the teaching of their specification, Applicants submit that nothing more than routine experimentation would be required to make and screen for mutated GPCRs useful in the claimed invention. For the reasons set forth here, Applicants submit that the specification enables the full scope of the claims. They request reconsideration and withdrawal of the rejection.

B. <u>The Specification Fully Describes the Claimed Invention</u>

The Office rejects claims 26, 52, 70-80, 82, 83, and 85 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably to those of skill in the art that Applicants were in possession of the claimed invention at the time the application was filed. Office action, page 7. Applicants traverse the rejection.

The Office acknowledges that "[t]he specification teaches oligonucleotides used to mutate or delete portions of a G-protein alpha subunit (SEQ ID NO: 42-63, only a few of which have been shown to have a positive effect in the cell-proliferation assay (Figure 12)." Despite that teaching, the Office urges that "[t]he description of one or a few polynucleotides encoding a G-protein polypeptide is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides." Office action, pages 7 and 8.

Applicants admit to some difficulty in understanding the basis for the rejection in that it purportedly is based on the written description requirement of section 112, first paragraph, but makes reference to enablement (Office action, page 8, first full paragraph) and the use of the invention (*id.*, page 9, first line). They understand the basis of the rejection as an alleged lack of written description for the language "a constitutively active heterologous G protein-coupled receptor" recited in the claims. Applicants submit that language is adequately supported by the specification to comply with the written description requirement.

For example, the disclosure in the specification at page 13, line 15 to page 15, line 7, describe a number of mutations that yield a constitutively active G protein-coupled receptor. Those mutations may occur in (1) the domains proximal to and within the third intracellular loops of the GPCR and (2) the membrane spanning helices. For each of those regions, specific mutations are identified that produce a constitutively active GPCR.

On page 8, the Office states that "[i]n this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or protein domains that have not been adequately identified. There is not even identification of any particular portion of the structure that must be conserved." Applicants respectfully ask for clarification as the claims under rejection do not recite "percent identity" language.

In view of these remarks, Applicants submit that the claims are fully described by the specification. Thus, they request that the Office reconsider and withdraw the rejection.

III. The Claims Are Patentable Over the Cited References

A. Price

The Office rejects claims 26, 52, 70-79, 82, 83, and 85 under 35 U.S.C. § 102(b) as allegedly anticipated by L. A. Price *et al.*, Functional Coupling of a Mammalian Somatostatin Receptor to the Yeast Pheromone Response Pathway, Molecular and Cellular Biology, 15(11):6188-95 (1995) ("Price"). Office action, page 10. Applicants traverse.

The Office cites the discussion on page 6193 as "disclos[ing] chimeric G-protein subunits in yeast, including alpha subunits, the use of which results in a functionally greater response in heterologous GPCR's, and a positive response in a cell-based growth assay." *Id.*; citation omitted. Price, which is mentioned at page 4 of the specification, however, does not teach (or suggest) "a yeast host cell comprising a constitutively active heterologous G protein-coupled receptor" as recited in independent claims 13 and 26, and dependent claims 52-85.

To anticipate a claim a reference must, in addition to being enabling, teach each and every element of the claim. Price does not meet the latter requirement. Because Price does not teach (or suggest) all of the limitations of the rejected claims, Applicants request reconsideration and withdrawal of the rejection.

B. Imhof

The Office rejects claim 26 under 35 U.S.C. § 102(b) as allegedly anticipated by M. O. Imhof *et al.*, Yeast RSP5 and Its Human Homolog hRPF1 Potentiate Hormone-Dependent Activation of Transcription by Human Progesterone and Glucocorticoid

Receptors, Molecular and Cellular Biology, 16(6):2594-605 (1996) ("Imhof"). Office action, page 10. Applicants traverse.

According to the Office, Imhof teaches in Figure 2 "an agonist assay in yeast cells comprising a heterologous human progesterone receptor and a mutated endogenous protein – RSP5 – that results in an improved functional response of the heterologous receptor." *Id.*, citation omitted. It concludes that "[t]his reference meets the limitations of claim 26, since claim 26 does not require a positive effect of the mutation on cell growth or proliferation." *Id.*

As noted above, claim 26 recites "a yeast host cell comprising a constitutively active heterologous G protein-coupled receptor." Like Price, Imhof does not teach (or suggest) that limitation. Accordingly, Applicants request that the Office reconsider and withdraw the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: March 22, 2005

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Attachments: One replacement sheet for Figs. 6A and 6B and one annotated sheet showing changes

AMENDMENTS TO THE DRAWINGS:

The attached sheet of drawings includes changes to the labels of Fig. 6. The upper panel of the drawing has been labeled "Fig. 6A." The lower panel has been labeled "Fig. 6B." No change to the substance of the drawings have been made.

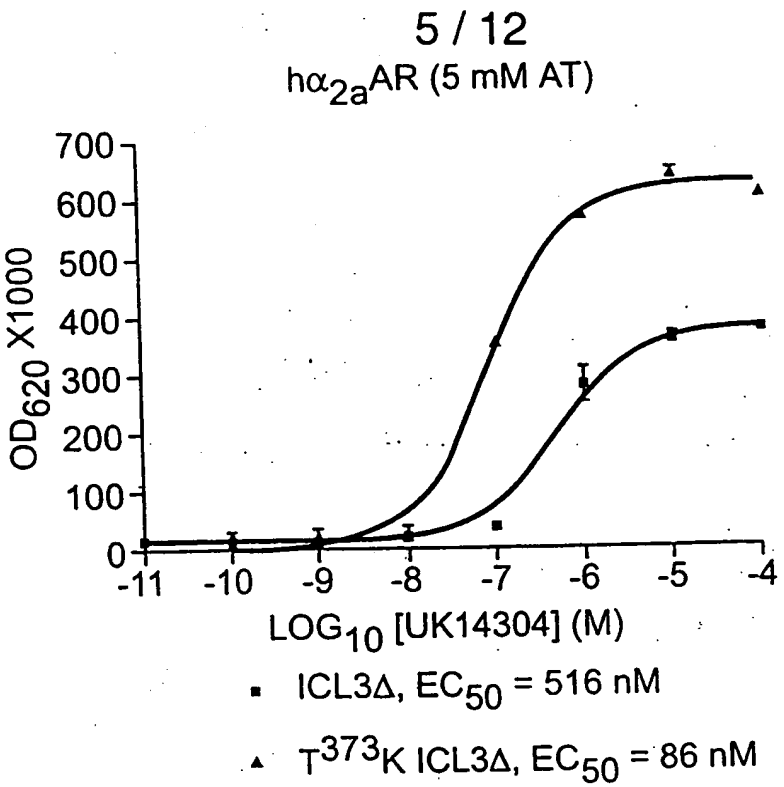

FIG. 6A

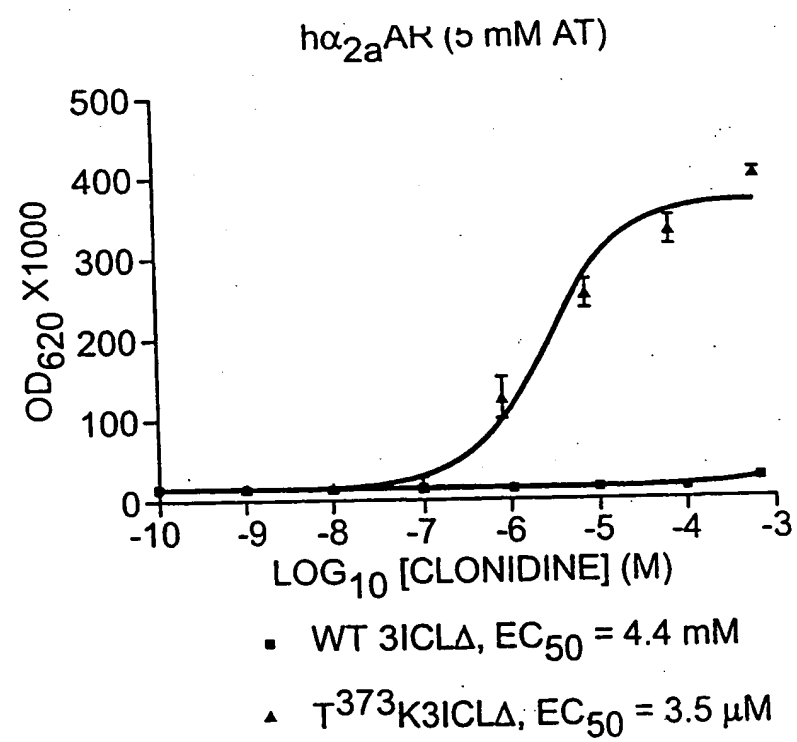

FIG. 6B